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# Cadaveric Hepatocytes Repopulate Diseased Livers: Life After Death

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#### Conflicts of interest

The authors disclose no conflicts.

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## Cadaveric Hepatocytes Repopulate Diseased Livers: Life After Death

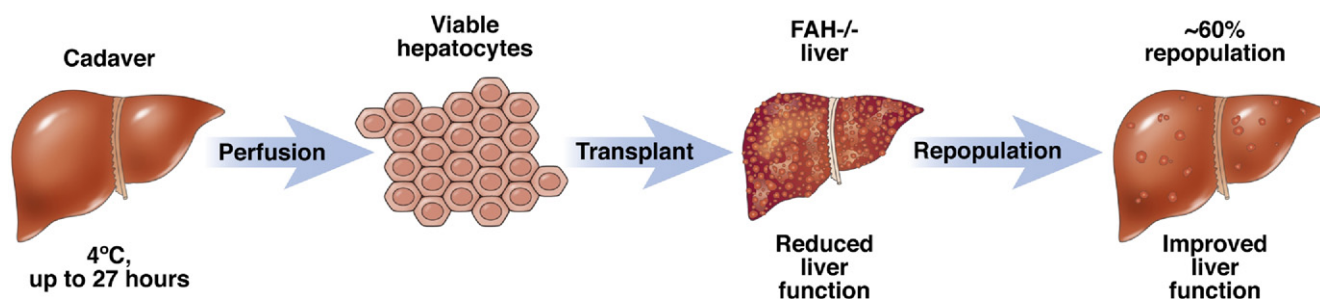
**See “Therapeutic liver reconstitution with murine cells isolated long after death,” by Erker L, Azuma H, Lee AY, et al, on page 1019.**

Presently, the only effective treatment for liver failure is solid organ transplantation. Although this approach is highly successful, it is limited by the short supply of donor organs. As such there is an imperative need to develop alternative therapies, such as cellular transplantation, to treat or “bridge” patients until a suitable organ can be sourced. Cellular therapy in animal models using adult human hepatocytes has demonstrated high repopulation efficiency with restoration of functional parenchyma<sup>1</sup> and may represent effective treatment for liver insufficiency as well as inherited metabolic liver disease.<sup>2</sup> Although this strategy is promising, it is likewise limited by donor organ availability.

One potential pathway to circumvent this problem would be to expand hepatocytes *ex vivo* in culture. Unfortunately, *ex vivo* hepatocytes are notoriously unstable and begin to dedifferentiate upon isolation, even in the presence of complex growth media.<sup>3</sup> Immortalization strategies have therefore been applied to primary hepatocytes in an attempt to overcome this problem but have remained unsuccessful.<sup>4</sup> In addition, such an approach

might create added complexity to direct utility in the clinic because genetic modification to achieve a proliferative state may result in a failure of contact inhibition and self-limiting proliferation *in vivo*. Because of the intrinsic problems with primary human hepatocytes several groups have focused on the role that stem cell populations might have in the production of large amounts of human hepatocytes for therapeutic purposes. The fetal and the adult liver provide ideal systems in which to purify potential stem cell populations. However, these populations are low in number, thereby making their isolation, purification, and large scale expansion challenging.<sup>5</sup>

More recently, there has been an emphasis on generating hepatocytes from pluripotent stem cell populations that are amenable to large scale production. The generation of hepatocytes from human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) has been demonstrated *in vitro*.<sup>6–10</sup> Moreover, iPSC technology<sup>11,12</sup> has allowed the creation of an autologous pluripotent stem cell population that has a number of advantages.<sup>13</sup> Although iPSC technology is promising, there are a number of significant impediments before clinical implementation.<sup>13</sup> This holds true also for hESCs with the recent decision by the Food and Drug Administration to put in abeyance the first hESC safety trial.<sup>14</sup>



**Figure 1.** Cadaveric hepatocytes efficiently repopulate diseased livers.

Problems with pluripotent stem cell derived hepatocyte transplantation have been also observed *in vivo*. The most advanced study to date has employed a mature population of hepatocytes for *in vivo* studies. Although this population of cells eliminated the development of teratomas or tumors in the liver, recipient animals developed peritoneal tumors,<sup>7</sup> demonstrating the need for improved stem cell-derived resources before safe clinical deployment. Therefore, the use of cell-based therapies from pluripotent stem cell-derived hepatocytes in routine clinical practice is not imminent. However, there are a number of near term gains using this technology that have important roles to play in medicine; extracorporeal strategies to bridge patients until liver transplantation or promote endogenous organ repair and the development of safer testing platforms for drug testing. Therefore, there is a major drive to find reliable sources of pluripotent stem cell-derived hepatocytes to meet this demand.<sup>13</sup>

Given the current safety concerns with transplanting pluripotent stem cell derived hepatocytes, the study by Erker et al<sup>15</sup> in this issue of *GASTROENTEROLOGY* is of great interest to the field. The study provides evidence that cadaveric liver tissue possesses clinical potential for therapeutic liver repopulation, radically changing the way in which we view the utility of this type of liver tissue.<sup>15</sup> Previously, non-heart-beating donors have been considered as a source of transplantable hepatocytes, but only if the livers were harvested under controlled conditions within 45 minutes of death.<sup>16</sup> Erker et al<sup>15</sup> digested livers, up to 27 hours post mortem, purifying cells suitable for transplantation, which was nearly as efficient as with freshly isolated hepatocytes. Moreover, Erker et al<sup>15</sup> demonstrated also that a similar type of cell population could be isolated from human resected liver tissue and could therefore be a potential source of hepatocytes for treating human liver disease (Figure 1). This is very important given the current shortage of transplantable human hepatocytes and may facilitate the development of novel treatment strategies that was previously inconceivable. Although this study demonstrates enormous potential, there are some issues that need to be addressed in future studies before this technology can be safely deployed in

the clinic. The hepatocyte population had a selective advantage in the described animal model. Therefore, questions remain about the ability of cadaveric hepatocytes to repopulate livers in an environment where the cells do not have a selective advantage and/or are exposed to inflammatory mediators in response to drug-, alcohol-, or viral-induced liver injury.

In conclusion, this study represents a vital step forward toward the use of cadaveric hepatocytes in the clinic. This study will undoubtedly stimulate interest in the utility of human livers from unanticipated deaths and emphasizes there is >1 solution to the challenge of generating high-fidelity human hepatocytes. Moreover, this study reinforces the notion that different methods of deriving human hepatocytes may suit differing clinical scenarios. As such, we are looking forward to future studies assessing the performance of human cadaveric hepatocytes in immunocompromised FAH<sup>-/-</sup> mice and immune-compromised models of acute and chronic liver injury.

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**Conflicts of interest**

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